INVESTIGATION OF CERTAIN CONSTITUENTS

OF THE URINE AND BLOOD

IN

ALTERNATING OR RECURRENT MENTAL STATES.

BY

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The object of this paper is an attempt to discover whether there may be any correspondence between alterations in the metabolic processes of the body, as indicated (1), by the excretion of certain substances in the urine; (2), by the numbers of the white corpuscles of the blood; and (3), by the condition of the blood-pressure, and alterations in the general mental state, in certain cases of mental disease in which periodicity or alternation is a prominent sign.

As will be seen, the cases examined, (twelve in number), have not been taken from one form of mental disorder. It was thought that more or less regularly recurring attacks of psychomotor acceleration, whether occurring as part of a definite cycle, as in Folie Circulaire, or as intermittent but still regular periods of excitement in the course of a Chronic Mania going on to terminal dementia, or as outbursts of excitement in the more rapid progress of a case of Dementia Praecox, might all conceivably be due to the

same or similar physical causes, and with a view to if possible finding some indication of the nature of this factor, the investigations alluded to were carried out. Below follows a detailed account of the investigations.

Patients selected for examination.

These were twelve in number and were all women. Their ages varied from 25 to 67 years - the average being 48½ years. The duration of illness varied from twenty-two months to 30 years - the average being 10½ years.

Below is a chart (Table 1) giving the details of each case. A rough estimate is given of the average length of each phase in each case. Owing to the fluctuations in this however, the duration mentioned can only be regarded as approximately correct.

Table 1.

Giving information as to patients examined:

Case	Age.	Duration of Mental Illness.	Average duration of cycle.				Nature of Mental Illness.	Notes.
			Total	Excited	Depressed	Lucid		
	Years	Years	Months.					
A	50	1 10/12	2-3	1½	¼	½	Recurrent Mania.	Very violent excitement. "Depression" = exhaustion
B	67	30	5-6	4		2	" "	
C	54	14	3	1		2	" "	
D	46	7	2-4	1½	¼	1	" "	"Depression" = exhaustion
E	37	4	2-3	2		1	Dementia Praecox.	See Note.
F	66	9	6	3	2	1	Folie Circulaire.	Patient passes from excitement into stupor, & later shows depression
G	48	4	5-6	2	2	2	" "	
H	50	25	3	1	1	1	" "	
I	44	9	-	-	-	-	" "	The phases in this case are so variable that I have not attempted to assign even an approximate figure.
J	30	6	9-12	6	2	4	" "	
K	25	8	9	6		3	Dementia Praecox.	
L	63	9	4-5	2		2	Recurrent Mania.	

It will be seen that some of the cases shew a quite definite period of psychomotor retardation or depression. As this phase did not occur in all, however, it was disregarded and no observations were made concerning it. In two of the cases of Folie Circulaire a short (12 - 48 hours) sharp period of depression precedes the development of the stage of psychomotor acceleration. In all the other cases the patient passes directly into a condition of excitement.

Further notes on cases.

A. During her attacks suffers from exceedingly severe excitement. Is noisy, restless, destructive, sleepless and violent. The following exhaustion is quite marked.

E. The exact mental condition in this case is a little obscure. For the last four years the patient has been subject to short but frequently recurring attacks of extremely vivid hallucinations both of sight and hearing, or a painful and distressing nature. Her reaction to these varies from time to time, but as a rule there is a depressed emotional tone, associated with restlessness and resistiveness. On the occasion of this examination she exhibited, as she sometimes does, a considerable degree of excitement and extreme restlessness. During the more lucid phases she is beginning to shew a slowly advancing deterioration in speech and conduct, and a loss of the finer instincts. The well-marked periodicity of her exacerbations is

the excuse for her inclusion in this series.

F. In this case the stage of depression is associated with very well-marked stupor.

K. This patient is a katatonic with fairly regular outbursts of moderately severe excitement. Mental deterioration is only of slight degree.

Description of Tests employed.

Three estimations of the leucocytes and of the blood-pressure were made, on alternate days, between 11 a.m. and 12 noon, and as far as possible under identical conditions. The figures given are the averages of the three results.

The urine tests were made in all cases on 24 hour specimens, on the day following collection. As the results were to be examined collectively and not singly, no estimation of the constituents of the diet was made. The standard house dietary was given in all cases before and during the tests, and this was the same both qualitatively and quantitatively during both phases of the illness.

The white blood corpuscles were counted on the Thoma-Zeiss slide. The blood-pressure was taken on Hill and Barnard's modification of the Riva-Rocci Sphygmomanometer.

The urea was estimated by Doremus' instrument; the Chlorides by Mohr's method, using Nitrate of Silver, with Chromate of Potash as an indicator; the Phosphates by titration with Nitrate of Uranium; and the Ethereal Sulphates by means of Barium Chloride and Hydrochloric

Acid.

The amount of urine passed in 24 hours is given in fluid ounces. The quantities of urea, chlorides and phosphoric anhydride are given in grammes. The results of the tests for ethereal sulphates were divided into three arbitrary classes, according to the density of the precipitate produced on heating the solution with the acid. In class 1, I put the cases in which there was either no reaction, or only a faint cloud; in class 2, those in which the precipitate was distinct; and in class 3, those in which there was a well-marked reaction.

In the Indican tests, a cobalt-blue colour, as suggested by Bruce[1] was taken as representing a normal amount. Any tint lighter than this is indicated by -, and any darker by +. Before making these 2 tests, all specimens which were less than 60 oz. for the 24 hours were diluted to this quantity with water.

Both blood and urine examinations were made when the patient's mental condition, whether of excitement or comparative lucidity, was quite definitely established, and not during the transition from one phase to another.

Below are set out the tables giving the results of the various tests. The letters L and E at the heads of the columns indicate the lucid and excited phases respectively.

Table II.

Table giving results of examination of the urine.

	Amount in Ounces.		Specific Gravity.		Urea. grms per day.		Chlorides. grms per day.		Phosphoric Anhydride. grms per day.		Ethereal Sulphates.		Indican.	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
a.	50	42	1017	1020	26·2	24·7	17·	19·4	2·3	2·1	1	1	+	-
B.	55	50	1015	1015	21·9	23·	14·6	14·2	2·6	2·4	2	1	+	+
C.	36	40	1017	1019	17·6	20·6	9·4	16·1	2·7	1·8	1	2	-	+
D.	86	52	1012	1023	27·7	33·6	12·2	7·7	1·7	2·1	1	3	-	+
E.	42	54	1020	1024	32·4	29·1	15·9	9·4	1·8	2·1	1	3	+	+
F.	21	30	1024	1018	24·9	18·1	14·9	19·4	2·8	1·4	1	1	-	-
G.	35	30	1017	1018	33·9	36·5	10·1	12·3	1·5	1·8	2	1	+	+
H.	64	45	1012	1018	26·4	19·1	6·7	13·2	1·5	1·4	2	2	-	-
I.	45	48	1020	1026	38·2	28·6	14·9	6·2	2·2	2·1	3	2	-	+
J.	52	42	1025	1020	35·5	25·9	11·3	9·1	3·	2·4	2	2	+	-
K.	35	47	1026	1022	39·5	33·8	8·7	5·9	2·2	2·9	1	2	-	-
L	40	48	1017	1021	31·9	28·4	7·9	13·2	1·4	1·6	1	3	-	-

Table III.

Table giving results of examinations of the blood.

	Blood-pressure in mm. Hg.		Leucocytes.	
	L	E	L	E
A.	135	130	8·500	9·400
B.	160	140	11·100	12·400
C.	135	145	12·200	8·800
D.	190	135	7·100	8.500
E.	175	155	9·000	10·400
F.	140	120	14·100	11·600
G.	130	150	10·800	9·700
H.	140	150	12·700	15·900
I.	125	125	9·800	17·600
J.	110	115	14·800	19·400
K.	115	110	8·300	6·700
L.	120	135	7·900	14·100

Remarks on Tables 11 and 111.

I was unable to ascribe any cause for the unusually large quantity of urine passed by case D.

Casting one's eye over the table, it is rather striking how consistent the urea figures are, - few cases shewing a variation of more than a few grammes. On the other hand, the variations in the Chlorides column are striking, being in case I more than 100%, and in several others, nearly as much. The phosphate excretion also remains fairly constant during the two phases, though in F there is a very marked drop. Both the ethereal sulphates and the indican are disappointing, in that they are found almost as frequently and plentifully in the lucid as in the excited phase. In cases I and L, a fairly well-marked deposit of ethereal sulphates occurred, although the indican reaction was not sufficiently definite to be called positive.

With regard to table 111, one at once notices the uniformly high pressure figures. This may be due to the high average age, viz. 48½ years, but at any rate all the tests were made under similar conditions, and with the same instrument, so that the results should be trustworthy for comparison with one another.

In cases C and I (during excitement) as the figures first obtained seemed unusual, fresh counts were made, but in both cases the former results were confirmed.

Case I is the only one which shews exactly the same blood-pressure in the two stages, though many

Table IV.

Below are Summaries of Tables II & III.

Amount in Ounces.		Specific Gravity.		Urea.		Chlorides.		Phosphoric Anhydride.		Ethereal Sulphates.		Indican.	
♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Five Cases of Recurrent Mania.													
53·4	46·4	1015·6	1019·6	25·0	26·0	12·2	14·1	2·1	2·	1·2	2·	2+	3+
Five Cases of Folie Circulaire.													
43·4	39·0	1019·6	1020·0	31·8	25·6	11·6	12·0	2·2	1·8	2·0	1·6	2+	2+
Two Cases of Dementia Praecox.													
38·5	50·5	1023	1023	35·9	31·0	12·3	7·6	2·0	2·5	1·	2·5	1+	1+
Total Averages for twelve Cases.													
46·7	44·0	1018·5	1020·3	29·6	26·8	12·0	11·2	2·1	2·0	1·5	2·0	5+	6+

Table V.

	Blood Pressure.		Leucocytes.	
	♂	♀	♂	♀
Five Cases of Recurrent Mania.	148	134	9360	10·640
" " " Folie Circulaire.	129	132	12·440	14·840
Two " " Dementia Praecox.	145	132	8650	8550
Total Averages	141	133	10·150	11·330

shew only a slight change. Case D on the other hand shews a remarkable drop of 55 mm. Hg, while G shews a rise of 20 mm. It is noticeable that the leucocytosis in D is very low in both phases.

Remarks on Summaries (Tables 1V and V.)

On examining these two tables of averages it will be seen that the figures shew much less striking variations, as is only to be expected. I have taken together the five cases of Folie Circulaire, the five of Recurrent Mania, and the two of Dementia Praecox. In the cases of Folie Circulaire, one finds that there is a very slight increase in the chloride-excretion, a more marked diminution in the phosphates, and a definite fall in the urea. The quantity and specific gravity are practically unchanged; there was a slight decrease in the excretion of the ethereal sulphates, while indican was present just as often during lucidity as during excitement.

In the cases of Recurrent Mania, there was quite a marked fall in the amount, and a consequent rise in specific gravity, during the phase of psychomotor acceleration. The phosphates shew a very slight fall, and the chlorides, ethereal sulphates and urea a more marked rise. Indican was found in excess in 3 cases, during the excited stage, as against 2 in the lucid stage.

In the two cases of Dementia Praecox, the amount

the phosphates and the sulphates shew more or less marked increases, while there is a striking fall in the chlorides, and a definite decrease in the urea.

In Table V. we find a distinct fall in the blood-pressure in recurrent mania and in dementia praecox, while there is a slight rise in the folie circulaire group.

The leucocytes do not vary so uniformly. The Recurrent Mania cases shew a moderate rise, the Folie Circulaire a more definite rise, while the Dementia Praecox remain practically the same. The total average shews a rise of about 1200 per c.mm.

Findings.

We find therefore as a result of the above examination of twelve mixed cases of Mental Disease, all shewing more or less regular periodicity and alternation, that there are certain changes in some of the constituents of the urine, in the blood-pressure and in the leucocytosis. We find that the amount of urine, the urea, the chlorides and the phosphorus shew a slight diminution, the specific gravity is slightly raised, the ethereal sulphates more definitely increased, and that Indican is present in six cases during the excited phase, as against five during the lucid period.

With regard to the blood-examination, we find a fairly definite fall of 8 mm. Hg. in the average blood-pressure, and a well-marked rise of 1200 in the leucocytes.

Deductions.

Examining these results with a view to drawing deductions as to the cause of the recurrent attacks of excitement in question, one is disappointed to find such slight changes in the urinary constituents examined. In fact as we are dealing with such a short series of cases, it is unjustifiable to regard the slight changes found in the quantity, the urea, the chlorides, the phosphates, and the specific gravity as of any great significance. We may reasonably assume that in these respects, or, as indicated by these substances, metabolism is not appreciably altered during phases of excitement from its normal for each case.

Bruce[2] found in examining cases of acute and recurrent mania during the periods of excitement, that the nitrogenous excretion was in excess, and the chlorides of the urine diminished. He therefore compared these attacks to acute febrile illnesses. Jones[3] found phosphorus in excess in 25% of all cases of insanity on admission. Mairet[4] found the phosphatic excretion raised in states of mania. Folin and Shaffer[5] report a case in which there were variations in the excretion of phosphorus corresponding with variations in the mental condition of an alternating case.

On the other hand, Barnes[6] after exceedingly minute and careful examination of the urine in two cases shewing relapses, was unable to shew that

"there is at present any disturbance of the metabolism which bears any relation to the mental condition except the indirect one that during the 'abnormal' phase, undernutrition is evident". Folin[7] in almost the same words denies that there is any characteristic increase or diminution of any urinary constituents, as associated with any mental disorder. Feder[8] and Koch[9] have both shewn by estimating the total phosphorus of the nervous system that it is impossible that any conceivable quantitative change in this could appreciably directly influence the excretion of phosphates in the urine.

With regard to the excretion of ethereal sulphates and indican, or indoxyl-potassium sulphate, the results are little more enlightening. These represent certain aromatic bodies e.g. cresol, indol, phenol, &c., proceeding from the metabolism or destruction of protein, in combination with So_3. Normally not more than a trace of these is found in the urine. They are increased in cases, such as abscess, gangrene, etc., in which excessive katabolism of proteid material is going on, and in constipation, and in some febrile conditions.

Both the ethereal sulphates as a whole, and indican, are found to be slightly increased in my series of cases, in the phase of excitement. Taubert[10] found in a case of manic-depressive insanity a marked regular increase in the amount of indican at each maniacal stage. This was unaffected by intestinal antiseptics. His opinion was that both

the indicanuria and the excitement were due to some unknown cause. Baugh[11] on the other hand found no excess in the excited stages of manic-depression, and Townsend[12] concurs with this finding. Bruce[13] thinks that indoxyluria has an important bearing on states of melancholia, concluding in fact that these are due to indol-poisoning in some cases. Easterbrook[14] on the other hand affirms that indicanuria rarely signifies anything more than constipation, that it can be removed by treating the constipation, and that both the indicanuria and the constipation are more likely to be events than causes of the mental condition. In none of the cases of the present series was constipation allowed to be a serious factor, - that is to say, during the time of observation, if the patient's bowels had not acted by 7 p.m. on any day, an aperient was administered. Barnes[6] in the case alluded to above was unable to find any correspondence between the quantity of indican and ethereal sulphates excreted and the mental condition of his patient, and he thought it improbable that "an increased production of indol acting in a cumulative manner as a toxic agent should be the cause of the attacks".

Taubert's[10] case, however, in conjunction with my findings, indicates that the argument must be left open. Some factor, hitherto undiscovered, which may be the cause alike of the alteration in the mental condition and of increased or changed putrefactive processes as indicated by the elimination of the aromatic group, seems to be at work and may eventually be traced.

On turning to the results of the blood-observations, one finds them more definite and satisfying. In the first place there is a fairly substantial fall in the blood-pressure during the period of excitement. This is in agreement with the results stated by Craig[15] and by Bruce[16] although the latter says that the pressure is raised at first and diminished later. Turner[17] on the other hand found no relation between the blood-pressure and the emotional tone.

The leucocytes shew a marked increase of almost 1200 per c.cm. during the stage of excitement. This result agrees also with those of many other observers. Bruce,[16,18] Bruce and Peebles,[19] and Howard[20] all describe maniacal conditions as accompanied by hyperleucocytosis, both when occurring as isolated attacks of mania, and as phases in circular or recurrent insanity. Further, Barnes found hyperleucocytosis during the "abnormal" phases of his two dementia praecox cases, alluded to above, which shewed strongly-marked periodicity.

Fisher[21] admits that a hyperleucocytosis occurs in recurrent maniacal states, but asserts that it is due to the increased exercise and general muscular hyperactivity. This statement, since the increase in the leucocytes is found whether the patient is kept in bed or not, requires confirmation. Barnes[22] found a hyperleucocytosis during the stuporose period in a patient suffering from Folie Circulaire, in whom the stage of excitement was replaced by stupor.

We find then in this series of cases shewing periodicity, a definite relation between the condition

of the blood-pressure and leucocytes, and the mental condition. Of what nature is this relation? Is it one of cause and event, or do both phenomena proceed from the same cause, or is the relation purely fortuitous? The mass of evidence rules out the last hypothesis. Further investigation is required before one can definitely settle which of the first two is correct. Such variations as I have found to exist in connection with the blood in alternating cases of mental disease, are, in the case of physical disease, universally admitted to point to the action of a toxic agent, most probably of bacterial origin. Considering this, and the manner of reaction of the brain to known toxins as in the case of Delirium Tremens, General Paralysis, Uraemia, etc., one is justified in the surmise that the attacks presently investigated are also due to the action of a toxin, wherever and however produced.

CONCLUSIONS.

(1) I have found no evidence of metabolic change.

(2) The evidences of poisoning by the products of putrefaction in the bowel or elsewhere are slight and inconclusive.

(3) During the stage of excitement the same reactions occur as are found in known bacterial infections. Therefore there is presumptive evidence that this stage takes its origin in a toxaemia of this nature.

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